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(54) **TISSUE ADHESIVE AND SEALANTS AND METHODS FOR THEIR USE**

(57) A biocompatible composition for use in adhering a medical device to tissue comprising a component comprising a biocompatible polymer functionalized with biotin; and a separate component comprising a biocompatible polymer functionalized with avidin, and wherein the composition is suitable for in vivo contact with tissue.

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## Description

### CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 60/777,297 filed Feb. 28, 2006, the entire disclosure of which is incorporated by reference herein.

### TECHNICAL FIELD

**[0002]** The present disclosure relates to compositions containing macromers capable of forming a matrix and the use of compositions containing these macromers as surgical adhesives or sealants.

### DESCRIPTION OF RELATED ART

**[0003]** In recent years there has developed increased interest in replacing or augmenting sutures with adhesive bonds. The reasons for this increased interest include: (1) the potential speed with which repair might be accomplished; (2) the ability of a bonding substance to effect complete closure, thus preventing seepage of fluids; and (3) the possibility of forming a bond without excessive deformation of tissue.

**[0004]** Studies in this area, however, have revealed that in order for surgical adhesives to be accepted by surgeons, they must possess a number of properties. They must exhibit high initial tack and an ability to bond rapidly to living tissue; the strength of the bond should be sufficiently high to cause tissue failure before bond failure; the adhesive should form a bridge, preferably a permeable flexible bridge; and the adhesive bridge and/or its metabolic products should not cause local histotoxic or carcinogenic effects.

**[0005]** Several materials useful as tissue adhesives or tissue sealants are currently available. One type of adhesive that is currently available is a cyanoacrylate adhesive. However, cyanoacrylate adhesives can have a high flexural modulus which can limit their usefulness. Another type of tissue sealant that is currently available utilizes components derived from bovine and/or human sources. For example, fibrin sealants are available. However, as with any natural material, variability in the material is frequently observed.

**[0006]** It would be desirable to provide a biological adhesive and/or sealant that is fully synthetic and therefore highly consistent in its properties without the concern of viral transmission. Such a composition should be flexible and biocompatible and should be suitable for use as an adhesive or sealant.

### SUMMARY

**[0007]** Compositions containing both a biotin-containing component and an avidin-containing component are useful as adhesives and/or sealants in medical or surgi-

cal applications. In embodiments, the biotin-containing component may be a polymer (such as, for example, a polyethylene glycol) functionalized with biotin, and the avidin-containing component may be a polymer (such as, for example, a polyethylene glycol) functionalized with avidin. The biotin-containing component and avidin-containing component may be kept separate and mixed just prior to use. Once combined into a single composition, the biotin groups of the biotin-containing component and avidin groups of the avidin-containing component bond to form a gel matrix that may be useful in adhering tissue to tissue or adhering a medical device to tissue or sealing holes in tissue.

**[0008]** In other embodiments, methods of adhering tissue to tissue are provided herein by applying a composition containing both a biotin-containing component and an avidin-containing component to approximated tissue. In other embodiments, methods of adhering a medical device to tissue are provided herein by applying a composition containing both a biotin-containing component and an avidin-containing component to the medical device or to tissue. In other embodiments, methods of sealing a hole in tissue are provided herein by applying a composition containing both a biotin-containing component and an avidin-containing component to a tissue defect.

**[0009]** In yet other embodiments, solid medical devices are formed from a composition containing both a biotin-containing component and an avidin-containing component.

**[0010]** In yet other embodiments, an apparatus is provided that includes a first chamber containing a first composition comprising a biotin-containing component, a second chamber containing a second composition comprising an avidin-containing component, and one or more outlets for simultaneously dispensing the first and second compositions.

### DETAILED DESCRIPTION

**[0011]** The present disclosure relates to a composition for use as a tissue adhesive or sealant, which is biocompatible and non-immunogenic. The composition can be employed to adhere tissue edges, seal air/fluid leaks in tissues, adhere medical devices to tissue and for tissue augmentation such as sealing or filling voids or defects in tissue. The composition can be applied to living tissue and/or flesh of animals, including humans.

**[0012]** While certain distinctions may be drawn between the usage of the terms "flesh" and "tissue" within the scientific community, the terms are used interchangeably herein as referring to a general substrate upon which those skilled in the art would understand the present adhesive to be utilized within the medical field for the treatment of patients. As used herein, "tissue" may include, but is not limited to, skin, bone, neuron, axon, cartilage, blood vessel, cornea, muscle, fascia, brain, prostate, breast, endometrium, lung, pancreas, small intestine,

blood, liver, testes, ovaries, cervix, colon, stomach, esophagus, spleen, lymph node, bone marrow, kidney, peripheral blood, embryonic or ascite tissue.

**[0013]** The composition of the present disclosure includes a component having at least one biotin group, or a derivative thereof, and a component having at least one avidin group, or a derivative thereof. The biotin moiety on the one component and the avidin group on the other component bond to one another thereby providing the present compositions. When the two components are combined, the composition rapidly forms a three dimensional gel-like adhesive matrix. The composition may, in embodiments, be utilized as an adhesive or sealant. The composition can also act as a drug carrier, allowing controlled release and direct delivery of a drug to a specific location in an animal, especially a human. Each component is preferably synthetic to reduce or eliminate immuno-reactions in a subject's tissue.

**[0014]** Biotin (also known as vitamin H, coenzyme R) is a readily water-soluble substance found at low concentrations in blood and tissues. Biotin acts as a carrier of activated CO<sub>2</sub> and permits the transfer of CO<sub>2</sub> to acceptors without the need for additional free energy. Activated carboxybiotin is usually attached to an enzyme that is required for the formation of carboxybiotin. For example, biotin may be attached to pyruvate carboxylase which, in the presence of acetyl CoA, catalyzes the formation of carboxybiotin and the subsequent transfer of the activated carboxyl group to pyruvate, to form oxaloacetate.

**[0015]** The biotin-containing component can be any biocompatible compound that includes one or more biotin moieties. The compound can be any small molecule or polymer capable of being functionalized. The biotin-containing component can be bioabsorbable or non-bioabsorbable. In some embodiments, the biotin-containing component may be derived from a polysaccharide. Suitable polysaccharides include, for example, sorbitol, mannitol, sucrose, dextran, cyclodextrin, combinations thereof, and the like. In other embodiments, the biotin-containing component may be derived from a polyalkylene oxide ("PAO"). Suitable PAOs include, but are not limited to, polyethylene glycol ("PEG"), polyethylene oxide ("PEO"), polypropylene oxide ("PPO"), a polyethylene glycol with lactide linkages, polypropylene glycol ("PPG"), co-polyethylene oxide lock or random copolymers, and poloxamers such as polyethylene oxide (PEO) copolymers with polypropylene oxide (PPO) such as the triblock PEO-PPO copolymers commercially available as PLURONICS(R) from BASF Corporation (Mt. Olive, N.J.). Various forms of PAOs, including functionalized PEGs, are also commercially available from providers which include, for example, Shearwater Polymers, Inc., Huntsville, Ala., and Texaco Chemical Company, Houston, Tex. In embodiments, combinations of the foregoing PAOs may be utilized.

**[0016]** In some embodiments, the biotin-containing component includes a bioabsorbable polymer. A bioab-

sorbable polymer breaks down in the body and may be gradually absorbed or eliminated by the body by hydrolysis, metabolic processes, or bulk or surface erosion. Examples of bioabsorbable materials suitable for making the biotin-containing component include, but are not limited to, polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrateco-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, polyamino acids (including, but not limited to, polyglutamic acid, polyaspartic acid, and synthetic amino acids with pendant acidic groups, including those commercially available from Sigma-Aldrich (St. Louis, Mo.), absorbable cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. In some embodiments, combinations of the foregoing bioabsorbable materials may be utilized. For example, one or more of the foregoing absorbable polymers can be reacted with a PAO to provide a degradable polymer having hydrophilic properties which then can be functionalized with biotin to provide the biotin-containing component.

**[0017]** In some embodiments the biotin-containing component may be modified to produce a multi-functional material, i.e., one having a branched or star configuration. Methods for achieving branching are within the purview of those skilled in the art and include, for example, reacting the compound used to form the biotin-containing component with a multifunctional branching agent either prior to or after functionalization with biotin. Suitable multifunctional branching agents include, but are not limited to, tris(hydroxymethyl)aminomethane (also known as 2-amino-2-(hydroxymethyl)-1,3-propanediol), enterodiol, cyclodextrins, polysaccharides (e.g., sorbitols, mannitols, sucrose, dextrans, cyclodextrins, etc.) polyols, polyvinyl alcohols, combinations thereof, and the like.

**[0018]** In embodiments, the molecular weight of the biotin-containing component may be from about 200 to about 50,000, and in embodiments from about 500 to about 5,000.

**[0019]** Polymers and other compounds (e.g., small molecules) can be functionalized with biotin, i.e., biotinylated, according to any method within the purview of those skilled in the art. For example, PEG can be functionalized using those methods disclosed in Chapter 22 of Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, J. Milton Harris, ed., Plenum Press, NY (1992).

**[0020]** The avidin-containing component can be any biocompatible compound that has been functionalized with avidin, streptavidin or their derivatives. Thus, as used herein, an avidin-containing component can include one or more moieties derived from avidin, streptavidin or their derivatives. The compound can be any small molecule or a polymer capable of being functionalized. The

avidin-containing component can be bioabsorbable or non-bioabsorbable.

**[0021]** Avidin (a glycoprotein from chicken egg white) and streptavidin (from *Streptomyces avidinii*) are two related proteins that bind biotin with similar dissociation constants of about  $10^{-15}$  M. Avidin occurs naturally in a tetrameric form with four identical subunits, each having about 128 amino acid residues, six mannose residues, and three glucosamine residues, for a combined molecular weight of approximately 68,000. In addition to the ability of avidin and streptavidin to bind biotin, many of their physical properties are quite similar. Both, for example, are constructed of four non-covalently attached identical subunits, each of which bears a single biotin-binding site. The subunit Mr values are very similar. Moreover, several short stretches in the sequences of the two proteins are preserved, particularly two Trp-Lys stretches that occur at approximately similar positions.

**[0022]** Avidin, streptavidin and their derivatives, as well as methods for obtaining same, are within the purview of those skilled in the art. For example, modified avidins have been prepared, such as N-acyl avidins, e.g., N-formyl, N-acetyl and N-succinyl avidins. These derivatives of avidin reduce the charge of the protein, but they may all be prepared via covalent attachment to the available lysines of avidin. An alternative to lysine modification is the modification of arginines on avidin. In this case, the lysines are still available for subsequent interaction. Two different derivatives of avidin which are modified in this manner are commercially available. One, ExtrAvidin(R), can be obtained in various functionally derivatized or conjugated forms from Sigma Chemical Company (St. Louis, Mo.). A second, Neutralite Avidin(TM) (a product of Belovo Chemicals, Bastogne, Belgium), is a deglycosylated form of avidin obtained enzymatically, which exhibits a neutral pH and bears free lysine groups for further derivatization. Other avidin derivatives include those disclosed in U.S. Pat. Nos. 6,638,508 and 6,632,929, the entire disclosures of each of which are incorporated by reference herein.

**[0023]** In some embodiments, the avidin-containing component may be derived from a polysaccharide. Suitable polysaccharides include, for example, sorbitol, mannitol, sucrose, dextran, cyclodextrin, and the like, and combinations thereof. In other embodiments, the avidin-containing component may be derived from a polyalkylene oxide ("PAO"). Suitable PAOs include, but are not limited to, polyethylene glycol ("PEG"), polyethylene oxide ("PEO"), polypropylene oxide ("PPO"), a polyethylene glycol with lactide linkages, polypropylene glycol ("PPG"), co-polyethylene oxide block or random copolymers, and poloxamers such as polyethylene oxide (PEO) copolymers with polypropylene oxide (PPO) such as the triblock PEO-PPO copolymers commercially available as PLURONICS(R) from BASF Corporation (Mt. Olive, N.J.). Various forms of PAOs, including functionalized PEGs, are also commercially available from providers which include, for example, Shearwater Polymers, Inc.,

Huntsville, Ala., and Texaco Chemical Company, Houston, Tex. In embodiments, combinations of the foregoing PAOs may be utilized.

**[0024]** In some embodiments, a bioabsorbable polymer is used to prepare the avidin-containing component. A bioabsorbable polymer breaks down in the body and may be gradually absorbed or eliminated by the body by hydrolysis, metabolic processes, or bulk or surface erosion. Examples of bioabsorbable materials suitable for making the avidin-containing component include, but are not limited to, polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, polyamino acids (including, but not limited to, polyglutamic acid, polyaspartic acid, and synthetic amino acids with pendant acidic groups, including those commercially available from Sigma-Aldrich (St. Louis, Mo.), absorbable cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. In some embodiments, combinations of the foregoing bioabsorbable materials may be utilized. For example, one or more of the foregoing absorbable polymers can be reacted with a PAO to provide a degradable polymer having hydrophilic properties which then can be functionalized with avidin to provide the avidin-containing component.

**[0025]** In some embodiments the avidin-containing component may be modified to produce a multi-functional material, i.e., one having a branched or star configuration. Methods for achieving branching are within the purview of those skilled in the art and include, for example, reacting the compound used to form the avidin-containing component with a multifunctional branching agent either prior to or after functionalization with avidin. Suitable multifunctional branching agents include, but are not limited to, tris(hydroxymethyl)aminomethane (also known as 2-amino-2-(hydroxymethyl)-1,3-propanediol), enterodiol, polysaccharides (e.g., sorbitols, mannitols, sucrose, dextrans, cyclodextrins, etc.) polyols, polyvinyl alcohols, combinations thereof, and the like.

**[0026]** In embodiments, the molecular weight of the avidin-containing component may be from about 200 to about 50,000, and in embodiments from about 500 to about 5,000.

**[0027]** Polymers and other compounds (e.g., small molecules) can be functionalized with avidin using any method within the purview of those skilled in the art. For example, PEG can be functionalized using those methods disclosed in Chapter 22 of *Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications*, J. Milton Harris, ed., Plenum Press, NY (1992).

**[0028]** Each avidin or streptavidin binds one molecule of biotin. The unique feature of this binding is the strength and specificity of formation of the avidin-biotin complex.

The resultant affinity constant, estimated at  $1.6 \times 10^{15} > M^{-1}$  for avidin and  $2.5 \times 10^{13} > M^{-1}$  for streptavidin, is the highest known for a protein and an organic ligand. It is so strong that biotin cannot be released from the binding site, even when subjected to a variety of drastic conditions such as high concentrations of denaturing agents at room temperature, e.g., 6 M guanidinium hydrochloride, 3 M guanidinium thiocyanate, 8 M urea, 10% [beta]-mercaptoethanol or 10% sodium dodecyl sulfate. Under combined treatment with guanidinium hydrochloride at low pH (1.5) or upon heating ( $>70$ [deg.] C.) in the presence of denaturing agents or detergents, the protein may be denatured, and biotin can be dislodged from the disrupted binding site.

**[0029]** The biotin-containing component and the avidin-containing component may be prepared and stored separately prior to use. The biotin-containing component and/or the avidin-containing component can be stored neat. Alternatively, the biotin-containing component and/or the avidin-containing component can be stored as a dry powder that may be reconstituted (e.g., by mixing with water or other biocompatible solvent) immediately prior to use. Alternatively, the biotin-containing component and/or the avidin-containing component can be formulated into compositions containing water or some other biocompatible solvent and stored separately until application. For example, these formulations can be solutions, emulsions, dispersions. The concentrations of the biotin-containing component and the avidin-containing component in such formulations will vary depending upon a number of factors, including the types and molecular weights of the particular polymers used and the desired end use application, i.e., as an adhesive or sealant. In embodiments, the biotin-containing component and/or the avidin-containing component may be present in such formulations in amounts from about 5% to about 95% by weight of the composition, in embodiments from about 20% to about 80% by weight of the composition.

**[0030]** In some embodiments, the present compositions may contain one or more bioactive agents. The bioactive agent may be included within the formulation containing the biotin-containing component, the avidin-containing component, or both. Alternatively, the bioactive agent can be mixed with the biotin-containing component and/or the avidin-containing component immediately prior to use. The term "bioactive agent", as used herein, is used in its broadest sense and includes any substance or mixture of substances that may have clinical use. Consequently, bioactive agents may or may not have pharmacological activity per se, e.g., a dye. Alternatively a bioactive agent could be any agent which provides a therapeutic or prophylactic effect, a compound that affects or participates in tissue growth, cell growth or cell differentiation, a compound that may be able to invoke a biological action such as an immune response, or could play any other role in one or more biological processes.

**[0031]** Examples of classes of bioactive agents which may be utilized in accordance with the present disclosure

include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetics, cholinomimetics, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, antineoplastics, immunogenic agents, immunosuppressants, gastrointestinal drugs, diuretics, steroids, lipids, lipopolysaccharides, polysaccharides, and enzymes. It is also intended that combinations of bioactive agents may be used in the present compositions.

**[0032]** Suitable antimicrobial agents which may be included as a bioactive agent in the compositions of the present disclosure include triclosan, also known as 2,4,4'-trichloro-2'-hydroxydiphenyl ether, chlorhexidine and its salts, including chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate, silver and its salts, including silver acetate, silver benzoate, silver carbonate, silver citrate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine, polymyxin, tetracycline, aminoglycosides, such as tobramycin and gentamicin, rifampicin, bacitracin, neomycin, chloramphenicol, miconazole, quinolones such as oxolinic acid, norfloxacin, nalidixic acid, pefloxacin, enoxacin and ciprofloxacin, penicillins such as oxacillin and piperacil, nonoxynol 9, fusidic acid, cephalosporins, and combinations thereof. In addition, antimicrobial proteins and peptides such as bovine lactoferrin and lactoferricin B may be included as a bioactive agent in the compositions of the present disclosure.

**[0033]** Other bioactive agents which may be included as a bioactive agent in the compositions of the present disclosure include: local anesthetics; non-steroidal anti-fertility agents; parasympathomimetic agents; psychotherapeutic agents; tranquilizers; decongestants; sedative hypnotics; steroids; sulfonamides; sympathomimetic agents; vaccines; vitamins; antimalarials; anti-migraine agents; anti-parkinson agents such as L-dopa; anti-spasmodics; anticholinergic agents (e.g. oxybutynin); antitussives; bronchodilators; cardiovascular agents such as coronary vasodilators and nitroglycerin; alkaloids; analgesics; narcotics such as codeine, dihydrocodeinone, meperidine, morphine and the like; non-narcotics such as salicylates, aspirin, acetaminophen, d-propoxyphene and the like; opioid receptor antagonists, such as naltrexone and naloxone; anti-cancer agents; anti-convulsants; anti-emetics; antihistamines; anti-inflammatory agents such as hormonal agents, hydrocortisone, prednisolone, prednisone, non-hormonal agents, allopurinol, indomethacin, phenylbutazone and the like; prostaglandins and cytotoxic drugs; estrogens; antibacterials; antibiotics; anti-fungals; anti-virals; anticoagulants; anticonvulsants; antidepressants; antihistamines; and immunological agents.

**[0034]** Other examples of suitable bioactive agents which may be included in the composition of the present disclosure include viruses and cells, peptides, polypep-

tides and proteins, analogs, muteins, and active fragments thereof, such as immunoglobulins, antibodies, cytokines (e.g. lymphokines, monokines, chemokines), blood clotting factors, hemopoietic factors, interleukins (IL-2, IL-3, IL-4, IL-6), interferons ([beta]-IFN, ([alpha]-IFN and [gamma]-IFN), erythropoietin, nucleases, tumor necrosis factor, colony stimulating factors (e.g., GCSF, GM-CSF, MCSF), insulin, anti-tumor agents and tumor suppressors, blood proteins, gonadotropins (e.g., FSH, LH, CG, etc.), hormones and hormone analogs (e.g., growth hormone), vaccines (e.g., tumoral, bacterial and viral antigens); somatostatin; antigens; blood coagulation factors; growth factors (e.g., nerve growth factor, insulin-like growth factor); protein inhibitors, protein antagonists, and protein agonists; nucleic acids, such as antisense molecules, DNA and RNA; oligonucleotides; and ribozymes; naturally occurring polymers, including proteins such as collagen and derivatives of various naturally occurring polysaccharides such as glycosaminoglycans; peptide hydrolases such as elastase, cathepsin G, cathepsin E, cathepsin B, cathepsin H, cathepsin L, trypsin, pepsin, chymotrypsin, [gamma]-glutamyltransferase ([gamma]-GTP) and the like; sugar chain hydrolases such as phosphorylase, neuraminidase, dextranase, amylase, lysozyme, oligosaccharase and the like; oligonucleotide hydrolases such as alkaline phosphatase, endoribonuclease, endodeoxyribonuclease and the like. In some embodiments, where an enzyme is added, the enzyme may be included in a liposome or microsphere to control the rate of its release, thereby controlling the rate of degradation of the composition of the present disclosure. Methods for incorporating enzymes into liposomes and/or microspheres are within the purview of those skilled in the art.

**[0035]** A single bioactive agent may be utilized in the present compositions or, in alternate embodiments, any combination of bioactive agents may be utilized.

**[0036]** A variety of optional ingredients may also be added to the compositions of the present disclosure. A phospholipid surfactant that provides antibacterial stabilizing properties and helps dispense other materials in the compositions may be added to the compositions of the present disclosure. Imaging agents such as iodine or barium sulfate, or fluorine, can also be combined with the compositions of the present disclosure to allow visualization of the surgical area through the use of imaging equipment, including X-ray, MRI, and CAT scan.

**[0037]** Once obtained, the biotin-containing component and the avidin-containing component can be combined to form compositions of the present disclosure which, in embodiments, may be utilized as a biocompatible adhesive or sealant. In embodiments, the biotin-containing component and the avidin-containing component may be applied directly onto a tissue surface to form a three-dimensional crosslinked matrix as a result of the reaction between the biotin groups with the avidin groups.

**[0038]** Application of the present compositions, with or without other additives, can be done by any conventional

means. These include dripping, brushing, or other direct manipulation of the composition on the tissue surface, or spraying of the biocompatible composition to the surface. In open surgery, application by hand, forceps or the like is contemplated. In endoscopic surgery, the biocompatible composition can be delivered through the cannula of a trocar, and spread at the site by any device within the purview of those skilled in the art.

**[0039]** The biocompatible composition can also be dispensed from a conventional adhesive dispenser, which may provide mixing of the biotin-containing component and the avidin-containing component prior to dispensing. Such dispensers are disclosed, for example, in U.S. Pat. Nos. 4,978,336, 4,361,055, 4,979,942, 4,359,049, 4,874,368, 5,368,563, and 6,527,749, the entire disclosures of each of which are incorporated herein by reference. Thus, in embodiments, the present disclosure also relates to an apparatus that includes a first chamber containing a first composition containing a biotin-containing component, a second chamber containing a second composition containing an avidin-containing component, and one or more outlets for simultaneously dispensing the first and second compositions.

**[0040]** The biocompatible composition resulting from the mixture of the biotin-containing component and the avidin-containing component can be used in human and animal medical applications including, but not limited to, wound closure (including surgical incisions and other wounds), adhesives for medical devices (including implants), sealants and void fillers, and embolic agents. The biocompatible compositions can be used in a medical/surgical capacity in place of, or in combination with, sutures, staples, clamps and the like. Use of the present compositions can eliminate or substantially reduce the number of sutures normally required during current practices, and eliminate the subsequent need for removal of staples and certain types of sutures and thus can be particularly useful for use with delicate tissues where sutures, clamps or other conventional tissue closure mechanisms may cause further tissue damage.

**[0041]** In some embodiments, the biocompatible composition can be used to seal or adhere delicate tissue together, such as lung tissue, in place of conventional tools that may cause mechanical stress.

**[0042]** Additional applications of the biocompatible composition include sealing tissues to prevent or control blood, or other fluid leaks, at suture or staple lines. In another embodiment, the biocompatible composition can be used to attach skin grafts and position tissue flaps during reconstructive surgery. In still another embodiment, the biocompatible composition can be used to close tissue flaps in periodontal surgery. The resulting biocompatible composition can also be used to seal air and/or fluid leaks in tissue as well as to prevent post-surgical adhesions and to fill voids and/or defects in tissue. Alternatively, the present compositions can be cured into useful solid shapes such as, for example, anti-adhesion barriers, staple buttresses, suture pledgets, tissue

bulking devices, and the like. The present compositions can also be applied as a biocompatible coating to any desired medical device.

**[0043]** To effectuate the joining of two tissue edges, the two edges are approximated, the biotin-containing component is combined with the avidin-containing component and applied to the approximated edges, and the two components crosslink with each other thereby forming the biocompatible composition of the present disclosure. In other embodiments, the biotin-containing component may be applied to one tissue edge, the avidin-containing component may be applied to a second tissue edge, and the two tissue edges approximated so that the biotin-containing component is combined with the avidin-containing component, and the two components crosslink with each other thereby forming the biocompatible composition of the present disclosure. The crosslinking reaction is rapid, generally taking less than one minute. In this case the composition of the present disclosure can be used as an adhesive to close a wound, including a surgical incision. In such a case, the composition of the present disclosure can be applied to the wound and allowed to set, thereby closing the wound.

**[0044]** In another embodiment, the biocompatible composition of the present disclosure may be used to adhere a medical device to tissue, rather than secure two edges of tissue. In some cases the medical device may include a coating of the biotin-containing component, the avidin-containing component, or both. In some aspects, the medical device includes an implant. Other medical devices include, but are not limited to, pacemakers, stents, shunts and the like. In embodiments, for adhering a device to the surface of animal tissue, the composition of the present disclosure, or the individual components thereof, can be applied to the device, the tissue surface or both. The device, biocompatible composition (or components thereof), and tissue surface are then brought into contact with each other and the composition is allowed to set, thereby adhering the device and surface to each other.

**[0045]** The present biocompatible composition can also be used to prevent post surgical adhesions. In such an application, the biocompatible composition may be applied and cured as a layer on surfaces of internal tissues in order to prevent the formation of adhesions at a surgical site during the healing process.

**[0046]** When used as a sealant, the biocompatible composition of the present disclosure can be used in surgery to prevent or inhibit bleeding or fluid leakage both during and after a surgical procedure. It can also be applied to prevent air leaks associated with pulmonary surgery. The biocompatible composition can be applied directly to the desired area in at least an amount necessary to seal off any defect in the tissue and seal off any fluid or air movement.

**[0047]** The present biocompatible composition has a number of advantageous properties. The resulting biocompatible compositions of the present disclosure are

safe and biocompatible, possess enhanced adherence to tissue, are biodegradable, have enhanced hemostatic potential, have low cost, and are easy to prepare and use. By varying the selection of the polymer components, the strength and elasticity of the biocompatible composition can be controlled, as can the gelation time.

**[0048]** The biocompatible composition rapidly forms a compliant gel matrix, which ensures stationary positioning of tissue edges or implanted medical devices in the desired location and lowers overall required surgical/application time. The biocompatible composition exhibits little or no swelling upon gel matrix formation, and therefore retains the positional integrity of the aligned tissue edges and/or location of a medical device. The biocompatible composition forms strong cohesive bonds, based in part on the high affinity of biotin for avidin and/or streptavidin. It exhibits excellent mechanical performance and strength, while retaining the necessary pliability to adhere living tissue. This strength and pliability allows a degree of movement of tissue without shifting the surgical tissue edge. Additionally, the biocompatible composition is biodegradable, allowing the degradation components to pass safely through the subject's body.

**[0049]** It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

The invention may be described by reference to the following numbered paragraphs:-

1. A biocompatible composition comprising; a biocompatible biotin-containing component; and a biocompatible avidin-containing component, wherein the composition is suitable for in vivo contact with tissue.
2. A biocompatible composition as in claim 1, wherein the biocompatible biotin-containing component comprises a polymer.
3. A biocompatible composition as in claim 1, wherein the biocompatible biotin-containing component comprises a polymer selected from the group consisting of polyethylene glycols and absorbable polymers.
4. A biocompatible composition as in claim 1, wherein the biocompatible biotin-containing component comprises polyethylene glycol having a molecular weight of less than about 1000.
5. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polymer functionalized with avidin.

6. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polymer functionalized with streptavidin.

7. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polymer selected from the group consisting of polyethylene glycols and absorbable polymers.

8. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polyethylene glycol having a molecular weight of less than about 1000.

9. A biocompatible composition as in claim 1, wherein the biocompatible composition further comprises a bioactive agent.

10. An apparatus comprising:

a first chamber containing a first composition comprising a biotin-containing component;

a second chamber containing a second composition comprising an avidin-containing component; and

one or more outlets for simultaneously dispensing the first and second compositions.

## Claims

1. A biocompatible composition for use in adhering a medical device to tissue comprising:

a component comprising a biocompatible polymer functionalized with biotin; and  
a separate component comprising a biocompatible polymer functionalized with avidin,  
and wherein the composition is suitable for in vivo contact with tissue.

2. A biocompatible composition as in claim 1, wherein the biocompatible-polymer is selected from the group consisting of polyethylene glycols and absorbable polymers.

3. A biocompatible composition as in claim 1, wherein the biocompatible biotin-containing component comprises polyethylene glycol having a molecular weight of less than about 1000.

4. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polymer functionalized with streptavidin.

din.

5. A biocompatible composition as in claim 1, wherein the biocompatible avidin-containing component comprises a polyethylene glycol having a molecular weight of less than about 1000.

6. A biocompatible composition as in claim 1, wherein the biocompatible composition further comprises a bioactive agent.



EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 03/000234 A1 (UNIV NOTTINGHAM [GB]; SHAKESHEFF KEVIN MORRIS [GB]; SALEM ALI KARIMJEE) 3 January 2003 (2003-01-03) * claims; example 6 * -----	1-6	INV. A61L24/04 A61L24/10 A61K31/74 C09J189/00
X	WO 94/23759 A1 (IMMUNOMEDICS INC [US]) 27 October 1994 (1994-10-27) * page 4 - page 5; claims; examples * -----	1,4,6	
X	US 6 544 543 B1 (MANDRUSOV EVGENIA [US] ET AL) 8 April 2003 (2003-04-08) * columns 3,6; claims; examples * -----	1,4,6	
A	HUANG N-P ET AL: "Biotin-Derivatized Ppoly(L-lysine)-g-poly(ethylene glycol): A Novel Polymeric Interface for Bioaffinity Sensing", LANGMUIR, AMERICAN CHEMICAL SOCIETY, NEW YORK, NY; US, vol. 18, 12 May 2001 (2001-05-12), pages 220-230, XP002319473, ISSN: 0743-7463, DOI: 10.1021/LA010913M * the whole document * -----	1-6	TECHNICAL FIELDS SEARCHED (IPC) A61L
A	US 2005/281802 A1 (GONG GLEN [US] ET AL) 22 December 2005 (2005-12-22) * paragraphs [0005], [0007], [0014], [0025], [0032], [0040], [0041], [0043], [0103], [0109] * * paragraphs [0128], [0135], [0137]; claims * -----	1-6	
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 26 May 2016	Examiner Derrien, Anne-Cécile
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.

EP 16 15 9311

5 This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

26-05-2016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03000234 A1	03-01-2003	AU 2002314317 B2	02-10-2008
		CA 2456286 A1	03-01-2003
		CN 1543339 A	03-11-2004
		EP 1401400 A1	31-03-2004
		JP 2005502396 A	27-01-2005
		NZ 530749 A	27-01-2006
		US 2004241203 A1	02-12-2004
		WO 03000234 A1	03-01-2003
		ZA 200400467 A	08-04-2005
WO 9423759 A1	27-10-1994	AU 674580 B2	02-01-1997
		AU 6666694 A	08-11-1994
		CA 2161109 A1	27-10-1994
		EP 0695194 A1	07-02-1996
		JP H08509226 A	01-10-1996
		SG 46472 A1	20-02-1998
		US 5482698 A	09-01-1996
		WO 9423759 A1	27-10-1994
US 6544543 B1	08-04-2003	NONE	
US 2005281802 A1	22-12-2005	US 2005281802 A1	22-12-2005
		WO 2006009682 A2	26-01-2006

**REFERENCES CITED IN THE DESCRIPTION**

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

**Patent documents cited in the description**

- US 77729706 P [0001]
- US 6638508 B [0022]
- US 6632929 B [0022]
- US 4978336 A [0039]
- US 4361055 A [0039]
- US 4979942 A [0039]
- US 4359049 A [0039]
- US 4874368 A [0039]
- US 5368563 A [0039]
- US 6527749 B [0039]

**Non-patent literature cited in the description**

- Poly(ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications. Plenum Press, 1992 [0019] [0027]